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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference C1-A0415Y1P	FOR FURTHER ACTION		See item 4 below
International application No. PCT/JP2006/306803	International filing date (day/month/year) 31 March 2006 (31.03.2006)	Priority date (day/month/year) 31 March 2005 (31.03.2005)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

<input checked="" type="checkbox"/>	Box No. I	Basis of the report
<input type="checkbox"/>	Box No. II	Priority
<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

		Date of issuance of this report 03 October 2007 (03.10.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer	
Facsimile No. +41 22 338 82 70	Yoshiko Kuwahara e-mail: pt07.pct@wipo.int	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

Applicant's or agent's file reference C1-A0415Y1P		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/JP2006/306803	International filing date (day/month/year) 31.03.2006	Priority date (day/month/year) 31.03.2005	
International Patent Classification (IPC) or both national classification and IPC			
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA			

1. This opinion contains indications relating to the following items:

<input checked="" type="checkbox"/>	Box No. I	Basis of the opinion
<input type="checkbox"/>	Box No. II	Priority
<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/>	Box No. IV	Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
<input type="checkbox"/>	Box No. VI	Certain documents cited
<input type="checkbox"/>	Box No. VII	Certain defects in the international application
<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/JP2006/306803

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

the international application in the language in which it was filed

the translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

- a. type of material

a sequence listing

table(s) related to the sequence listing
- b. format of material

on paper

in electronic form
- c. time of filing/furnishing

contained in the international application as filed

filed together with the international application in electronic form

furnished subsequently to this Authority for the purposes of search

3. In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY			International application No. PCT/JP2006/306803																								
Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																										
<p>1. Statement</p> <table> <tr> <td>Novelty (N)</td> <td>Claims</td> <td>1-97</td> <td>YES</td> </tr> <tr> <td></td> <td>Claims</td> <td></td> <td>NO</td> </tr> <tr> <td>Inventive step (IS)</td> <td>Claims</td> <td></td> <td>YES</td> </tr> <tr> <td></td> <td>Claims</td> <td>1-97</td> <td>NO</td> </tr> <tr> <td>Industrial applicability (IA)</td> <td>Claims</td> <td>1-97</td> <td>YES</td> </tr> <tr> <td></td> <td>Claims</td> <td></td> <td>NO</td> </tr> </table>				Novelty (N)	Claims	1-97	YES		Claims		NO	Inventive step (IS)	Claims		YES		Claims	1-97	NO	Industrial applicability (IA)	Claims	1-97	YES		Claims		NO
Novelty (N)	Claims	1-97	YES																								
	Claims		NO																								
Inventive step (IS)	Claims		YES																								
	Claims	1-97	NO																								
Industrial applicability (IA)	Claims	1-97	YES																								
	Claims		NO																								
<p>2. Citations and explanations:</p> <p>Document 1: Sal-Man N. et al., Arginine mutations within a transmembrane domain of Tar, an Escherichia coli aspartate receptor, can drive homodimer dissociation and heterodimer association in vivo, Biochem. J., 01 Jan. 2005, Vol. 385 (pt 1), Pages 29 to 36, particularly, page 29, lower right column, line 6th from the bottom to page 30, left column, line 23</p> <p>Document 2: Kumar R. et al., The second PDZ domain of INAD is a type I domain involved in binding to eye protein kinase C. Mutational analysis and naturally occurring variants, J. Biol. Chem., 2001, Vol. 276, No. 27, Pages 24971 to 24977, particularly, page 24971, right column, lines 25 to 31; page 24974, left column, lines 4 to 11; Fig. 2</p> <p>Document 3: JP 2004-0866862 A (Celestar Lexico-Sciences Inc.) , 18 March 2004, Particularly, abstract; Fig. 8; Paragraph 0019 & US 2005/0130224 A1 & EP 1510943 A1 & WO 03/107218 A1</p> <p>Document 4: JP 11-500916 A (Genentech Inc.), 26 January 1999, Particularly, Claims; Figs. 1 to 4 & US 5731168 A & WO 96/027011 A1 & EP 812357 A1</p> <p>Based on the descriptions in documents 1 and 2 cited in the international search report and on common technical knowledge in the field (if necessary, see document 3), the inventions of claims 1-16, 24-40, and 48-67 lack an inventive step.</p> <p>Document 1 discloses that a dimer of Tar-1 can be brought about by a polar amino acid motif, and it states that interestingly, a mutant construct containing glutamic acid residues at positions 22 and 25, which is located at the interaction interface, was found to increase dimerization considerably. In addition, document 1 describes the fact that the effect of positively charged residues on self-assembly of the Tar-1 transmembrane domain in the body was investigated by replacing positions 22 and 25 with an arginine, and argues for the possible role of a mutation to arginine wherein homodomain formation is further inhibited, but heterodimer formation is not inhibited thereby.</p>																											

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The invention of claim 1 relates to an invention wherein polypeptide assembly is inhibited. As a specific method therefor, Claim 5 describes the alteration of nucleic acids so that two or more amino acid residues forming an interface will have the same type of charge.

However, the mutual interaction among proteins is assumed to be determined by various elements of the entire structure, including the amino acids forming an interface thereof, and as discovered in document 1, in the dimerization of Tar-1, dimerization is considerably increased with a mutant construct containing two glutamic acid residues at positions 22 and 25, which are located on the interaction interface. However, this authority does not find that it was common technical knowledge at the time this application was filed that if the amino acid residues forming an interface are given the same type of charge, the assembly of all polypeptides will be inhibited.

As a result, this authority finds that the inventions of claims 1-97, which do not specifically set forth the amino acid residues, sequences, and the like of mutated proteins, lack sufficient support by the DESCRIPTION.

WRITTEN OPINION OF THE
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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V.

Document 2 states that almost all PDZ interaction ligands have a hydrophobic residue (Ile, Leu, or Val) at the C-terminus thereof; that X-ray crystallographic analysis reveals that tetrapeptide ligand is affixed in the trough formed between the second β -chain and the second α -helix of the PDZ domain; individual PDZ domains appear to recognize unique C-terminal sequences; and whereas wild-type eye PKC exhibits more potent interaction than PDZ2, that interaction is dramatically reduced by substituting Glu or Lys for Ile (-3).

In addition, document 2 states that whereas the type I PDZ domain normally contains the basic residue His or Arg at the start of α B in order to bind to the type I target (Ser/Thr) (-2), the type II target contains an umbrella hydrophobic or Tyr residue at (-2) that interacts with an α B position hydrophobic residue (for example, Val) corresponding to the type II PDZ domain. Document 2 also states that the involvement of His 310 in PDZ2 α B was investigated by amino acid substitution following a pull down assay.

Documents 1 and 2 both concern methods wherein mutation was performed on an amino acid exhibiting interaction in assembly of a peptide such as in a dimer, between a domain and a ligand, etc., and because the effect of hydrophobicity, charge, and the like is important in the interaction of two peptides and it is common technical knowledge in this field to perform identification of the hydrophobic surface of a protein, identification of electrostatic interactive sites, identification of interactive sites, and the like (if necessary, see document 3), this authority finds that persons skilled in the art can easily conceive of controlling an interaction such as assembly and the like by identifying those interactive sites in polypeptides exhibiting various interactions other than those described in documents 1 and 2, and performing mutations on the amino acids located at those sites.

Based on the descriptions in documents 1 and 2 cited in the international search report and on widely known technology in the field (if necessary, see documents 3 and 4), the inventions of claims 17-23, 41-47, and 68-97 lack an inventive step.

Because producing a dimer-specific antibody that binds to both dimers having different antigen binding activity and performing a mutation of an amino acid residue of a polypeptide in contact with the interface member so that a heterodimer is formed during that process are widely known technology in this field (if necessary, see document 4). Therefore, this authority finds that applying the above technology to prepare a dimer-specific antibody presents no particular technical difficulty to persons skilled in the art.

In addition the DETAILED DESCRIPTION of this application states that formation of the homodimer is inhibited and the heterodimer formation rate is increased in mutants s1, s2, s3, and w1 of Table 1, but this authority finds that the inventions relating to claims encompassing mutants other than these do not provide an advantageous effect that cannot be predicted from the inventions described in the above documents and widely known technology.